

# Targeting Ref-1/APE1 Pathway Inhibition in Pancreatic Cancer Using APX3330 for Clinical Trials

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Pancreatic ductal adenocarcinoma is the 4th leading cause of cancer-related mortality in the US. Most patients present with advanced disease and ~95% die within five years, most surviving under six months. Targeted therapies offer modest improvement in survival, albeit at an increase in side effects and unwanted toxicities.

Ref-1 regulates transcription factors involved in pancreatic cancer cell survival signaling due to its redox-coactivator activity, such as HIF-1 $\alpha$ , NF $\kappa$ B, NRF2 and STAT3. High expression levels of Ref-1 indicate decreased survival in PDAC and other cancers. APX3330, a specific Ref-1 inhibitor, has been shown in multiple *in vitro* and *in vivo* pancreatic cancer models to be effective in reducing tumor growth and metastases. The safety and dose administration of APX3330 have been previously established, including toxicology, phase I, and phase II clinical evaluation in non-cancer patients in Japan (Eisai). We have partnered with ApeX Therapeutics to develop APX3330 for cancer treatment (phase I trial anticipated early 2016).

We studied interactions of Ref-1, APX3330, convergent pathways; i.e. HIF-1 $\alpha$  and STAT3, and downstream targets like CAIX. We performed *in vivo* studies demonstrating single and combination effects of APX3330 with Gemcitabine (Gem) showing significantly decreased tumor volume in the combination treatments. We also tested single and combination studies of APX3330 in an *ex vivo* 3-D tumor-stroma model system using patient derived tumor cells along with patient derived cancer-associated fibroblasts. We used the CAIX inhibitor SLC-0111 and JAK2 inhibitor, Ruxolitinib; both in clinical trials. In our system, APX3330 decreases the tumor area and intensity in a dose-dependent manner. The combination of APX3330 with Gem demonstrated an additive enhancement effect in the tumor, and APX3330 with SLC-0111/Ruxolitinib enhanced tumor killing. These data demonstrate APX3330 single agent efficacy in our 3D patient model and enhanced tumor killing when pathways regulated by Ref-1, HIF-1 and STAT3 are blocked.